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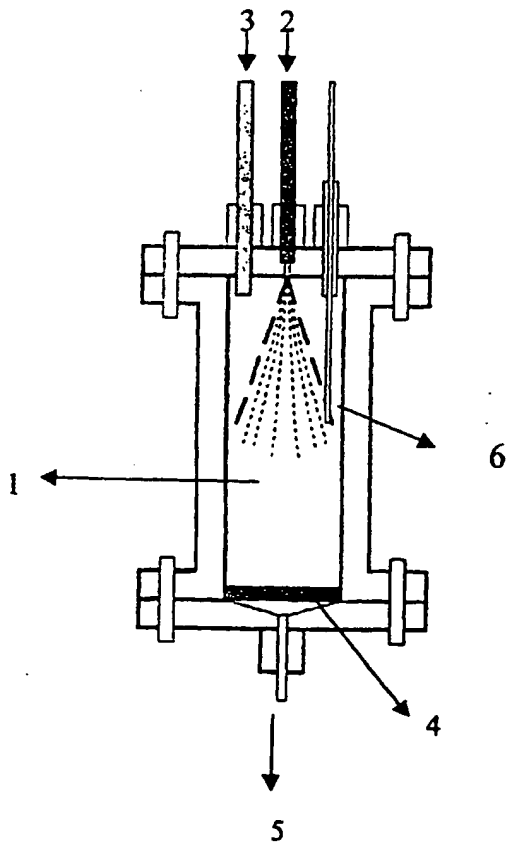
[Continued on next page]

(54) Title: MICRONIZED PHARMACEUTICALS



(57) Abstract: By means of the action of a supercritical fluid (SCF), for example supercritical carbon dioxide ($SCCO_2$), substances of pharmaceutical use are precipitated in form of amorphous or semicrystalline particles of micrometric or submicrometric dimensions. Said substances would most typically be sulfonamides or sulfones such as Nimesulide, dissolved in an organic solvent such as 1-methyl-2-pyrrolidone (NMP) or dimethylsulfoxide (DMSO). The process parameters are such as to maximise the solubility of the organic solvent in the SCF and minimize the solubility of the substance to be micronized in the SCF. The amorphous or semicrystalline state of the particles so obtained, allow one to enhance the pharmacokinetics of the substance.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

BACKGROUND OF THE INVENTION

1.Title

Micronized pharmaceuticals

2.Field of the invention

The present invention relates to the production of micronized pharmaceuticals, particularly sulfonamides and sulfones (eg. Nimesulide, N-(4-nitro-2-phenoxy-phenyl)methanesulfonamide, CAS 51803-78-2, Rofecoxib, 4-[4-(methylsulfonyl)phenyl]-3-phenylfuran-2(5H)-one, CAS 162011-90-7, Celecoxib, 4-[3-(1,1,1-trifluoromethyl)-5-(4-methylphenyl)-pyrazol-1-yl]-benzensulfonamide, CAS 169590-42-5) charactarized by amorphous or semicristalline particles of micrometric and submicrometric dimensions.

3. Description of Related Art

Numerous sulfonamides, sulfones and their derivatives posess pharmacological actions which classify them in as diverse therapeutic categories as analgesics, bacteriostatics, antibiotics, antihypertensives, antiinflammatories, antirheumatics, antipyretics and diuretics.

Among these there is Nimesulide which is a non steroidal anti inflammatory drug (NSAID) with analgesic and antiinflammatory properties. It is the active ingredient in numerous pharmaceuticals such as Nisulid, Aulin, Flogovital, Mesulid, Nimed, Sulidene. It is slightly soluble in water and posesses a moderate bioavailibility. One can partially correct this problem by producing it in form of its micronized sodium salt, by means of spray-drying or milling, in dimensions comprised between 5μm and 20μm (European Patent EP 937709 A1, 25.08.1999,(Helsinn Healthcare SA)). Nimesulide is a cyclooxigenase inhibitor, as are Rofecoxib (a sulfone) and Celecoxib (a sulfonamide). Cyclooxigenase is an enzyme involved in the synthesis of prostaglandins. Pharmacologic properties are in fact often attributable to a particular SAR (Structure Activity Relationship), and sulfonamide and sulfone functional groups are in effect bioisosteric. Structural similarity is also at the origin of similar

chemical and physical properties, and therefore of their behaviour in micronization processes carried out by means of the SAS technique, object of the present invention.

The pharmacokinetics of these active principles depends not only from their chemical and physical properties but also from the dimensions of the particles which constitute the solid.

The usual industrial synthesis methods produce crystalline solids, which are then subsequently micronizable by physical means (eg. jet milling). This method allows a reduction of the crystal diameter to 4-5μm, but with a very wide range in size, in the order of 20-30μm. Other techniques utilized to produce micronized powders with diameters of a couple of μm are: precipitation from liquids, plasma spray, freeze drying and spray drying.

These techniques have numerous disadvantages because they are limited as far as smallest obtainable particle size, they generate rather wide granulometric distributions and create problems associated with thermal stability and solvent residues. The particle size limit affects in turn the solubility and especially the speed of dissolution. This limitation has important consequences regarding the preparation of injectable solutions, the development of new applications for the active ingredient (eg. as an inhalable) and the pharmacokinetics.

With respect to the crystalline state, the amorphous state poses less of a hinderance to interactions between the solvent and the still to be dissolved solid.

The production of an amorphous state entails the solubilization of the substance in a solvent and its subsequent solidification in conditions which prevent crystal formation.

During the course of the last decade micronization techniques based on supercritical fluids have been developed, and these have allowed one to obtain micrometric and submicrometric particles with a controlled granulometric distribution. One of these techniques called Supercritical AntiSolvent (SAS) precipitation is based on the fact that the supercritical fluid insoluble substance one wants to micronize is dissolved in an organic solvent, which is soluble in the supercritical fluid. The organic solution is then brought in contact with the supercritical fluid, into which it swells. The solvent

then passes into the supercritical fluid. During this process the solute initially in the organic solution is released in form of particles. The speed of the process and the extreme dispersion of the precipitating solute preclude the formation of crystals, so that the solid precipitates in form of amorphous particles, which according to the conditions range from several hundred nanometers to several micrometers. The semi-continuous variant of this technique is described by Gallagher et al. (Supercritical fluids Science and Technology, ACS Symp. Series 406,1989, p. 334), the continuous one by Yeo et al. (Biotech. Bioeng., 41, 341 (1993)), and by Reverchon et al. ((Ind.Eng. Chem. Res., 34, 4087, (1995), Pat. It. ITSA970010 A 19970701 (0.-07.97) and finally the batch one by Debenedetti et al. (EP 0542314A1 (1992)).

The SAS technique has been successfully applied to proteins, explosives, solid propellants, polymers, superconducting ceramic precursors and pharmaceuticals such as antibiotics (eg. amoxycillin) and anti-asthmatics (eg. salbutamol).

The SAS technique has not yet been applied to the sulfonamides and sulfones.

This invention utilizes the SAS technique to produce sulfonamides, sulfones and their derivatives in form of amorphous or semicrystalline particles posessing dimensions between 100 nm and 3μm, for use in the production of pharmaceuticals.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig 1. Description of the apparatus utilized for the precipitation process:

1. Precipitation chamber for the micronized solid
2. Injector utilized for feeding the solution of substance to be micronized, with nozzle to atomize the solution
3. Injector for the supercritical fluid used as antisolvent
4. Porous frit to retain micronized powder and allow outflow of solvent and supercritical fluid utilized as antisolvent
5. Outlet for solvent and supercritical fluid utilized as antisolvent
6. Probe to measure temperature and pressure in the chamber listed under 1

Fig 2. SEM image of the micronized product

The product obtained by means of the SAS technique may be analysed by means of a scanning electron microscope to verify its dimensions, its degree of aggregation and its granulometric distribution. In this image one can see the particles obtained by means of the production method 1.

Enlargement: 50'000 x.

Scale: 1 mm = 40 nm

Fig 3. Granulometric distribution curve

By means of specific software (Sigma Scan 5.0) one obtains the granulometric distribution curve in form of a histogram (% total particles in function of particle diameter) from the SEM image.

Minimum diameter (smallest particle diameter): 121 nm

Maximum diameter (largest particle diameter): 385 nm

Mean diameter: 244 nm

Standard deviation from mean value: 5,3%

70% of the particles posesses a diameter between 190 nm and 300 nm

DESCRIPTION OF THE PREFERRED EMBODIMENTS

According to this invention sulfonamides or sulfones are produced in form of amorphous or semicrystalline micronized powders. One starts from a solution of the given sulfonamide or sulfone dissolved in an organic solvent (eg. dimethylsulfoxide (DMSO), 1-methyl-2-pyrrolidone (NMP), ethanol, acetone , ethyl acetate, dimethylformamide (DMF), etc...).

The apparatus to precipitate the micronized powder is decribed in Fig. 1. It allows one to perform the SAS technique as described in the literature (Reverchon, Della Porta, Taddeo, Pallado, Stassi, Ind. Eng. Chem Res., 34, 4087, (1995); Reverchon, Celano, Della Porta, Pace, Istituto Nazionale per la FISI (IT): Pat. It. ITSA970010 A

19970701 (0.-07.97); Reverchon, Celano, Della Porta, J. Mat. Res., Vol. 13, No.2, Feb 1998).

It consists of a precipitation chamber 1, posessing two independent inlets:

-the injector 2 to feed the solution of the substance to be micronized (solute) in a liquid solvent.

-the injector 3 to feed the supercritical fluid to be used as antisolvent.

The injector 2 has a nozzle at its extremity in order to atomize the solution on its entry into chamber 1. Chamber 1 also has a probe fixed into it in order to measure temperature and pressure in the particle forming region. The flow exiting from injectors 2 and 3 should preferably be parallel and flowing in the same direction as is shown in Fig. 1.

On the bottom of the chamber there is a porous frit , preferably made of sinterized material and having an apparent porosity lying preferably between 50 and 100 μm. It must be able to retain the particles and allow the outflow of the solvent and antisolvent through the outlet 5. The solution (solvent +solute) is fed by a first pump to the precipitation chamber 1 , and subsequently atomized (formation of microscopic droplets with diameter 20 to 120 μm) by passage through injector 2 and its nozzle. The very high surface area so obtained enables the interaction between solvent and supercritical fluid, which flows continually into chamber 1 by means of injector 3 which in turn is fed by a second pump. During its solubilization in the supercritical fluid the solvent augments its volume by a factor of between 10 and 100. At the same time the supercritical fluid aids the precipitation of the solute because they are mutually insoluble. The solid deposits itself on the porous frit 4 while the solvent and antisolvent are vented from outlet 5. The solvent is subsequently recuperated by allowing the spontaneous evaporation of the supercritical fluid. The feed of solvent and antisolvent by means of independent pumps, the pressurization of the supercritical fluid used as antisolvent, the solvent recovery and the eventual recycling of the supercritical fluid used as antisolvent are all carried out as is customary in supercritical fluid plant technology and as described in the literature (Reverchon, Celano, Dalla Porta, J.Mater. Res., Vol 13, No. 2, Feb 1998).

The micronizing effect depends on the speed of the expansion process and on the affinity the solvent has for the supercritical fluid. The nature of the chosen solvent and antisolvent, the antisolvent pressure and temperature as determined by means of probe 6, the solute concentration in the solution and the ratio between flow rate of solution and antisolvent are the factors that determine the dimensions and granulometric distribution of the particles produced. In the present invention DMSO, NMP, ethanol, ethyl acetate or DMF were utilized as solvents, while carbon dioxide, nitrous oxide, propane, ethylene, water or trifluoromethane in their respective supercritical phase were utilized as antisolvent. Flow rates comprised between 0,1 and 100 ml/min were utilized for the solution. The antisolvent flow rate was comprised between 1000 and 10000 ml/min expressed as gas at STP. The concetration of the solution was comprised between 1 and 20 mg/ml.

The physical state of the obtained product can be analyzed by means of scanning electron microscopy (SEM). The SEM image allows one to verify:

-the amorphous (typically in form of spheres) or crystalline (needles, cubes, or other geometric forms according to the nature of the substance) state

-the degree of aggregation

-the granulometric distribution of the micronized powder by means of a specific software (eg. Sigma Scan).

The information one is able to obtain from the SEM analysis allows one to optimize the process parameters (eg. pressure of supercritical fluid used as antisolvent, precipitation chamber temperature, solution concentration, flow ratio of solution and supercritical fluid used as antisolvent), in order to obtain the desired product characteristics (eg. mean particle diameter, granulometric distribution and degree of particle aggregation).

EXAMPLES

Production example 1.

By means of the SAS technique amorphous or semicrystalline Nimesulide particles were produced. The substance was dissolved preferably in 1-methyl-2-pyrrolidone (NMP). The resulting solution should posess a concentration comprised between 0,1 and 100 mg/ml, preferably 10 mg/ml.

The solution is fed into the chamber at a flow rate between 0,1 and 10 ml/min, preferably at 1 ml/min, at a density of 1100 kg/m^3, in quantities ranging from 20 to 50 ml, preferably 30 ml.

The antisolvent, preferably carbon dioxide, is fed into the chamber at a flow rate comprised between 1000 and 10000 ml(gas STP)/min, preferably at 8000 ml (gas STP)/min and at a pressure between 78 and 400 bar, preferably 85 bar and at a temperature between 30 and 60 °C, preferably 40 °C. The resulting ratio between flow rate of solvent and flow rate of antisolvent is 1,25 E-04. The product is finally washed by passing only antisolvent through the chamber for a period of time ranging from 60 to 100 min, preferably 80 min.

Results:

- Yield:

  The yield of recovered Nimesulide (300 mg) was higher than 95%.

- Identification based on physical data:

  The product collected from the bottom of chamber 1 was analyzed by means of scanning electron microscopy (SEM), with an magnification of 50000 X, resulting in Fig. 2.

  One is able to observe the remarkable homogeneity of the particle dimensions and their partial aggregation.

  The particle diameter and the granulometric distribution were obtained from the SEM image by means of specific software (Sigma Scan 5.0). The spherical shape of the particles is typical of their amorphous state, as this subtance has needle shaped crystals in the crystalline state.

The granulometric distribution curve is shown in Fig. 3 in form of a histogram. It depicts the number of particles (% particles) in function of particle diameter.
The granulometric distribution curve has the following characteristics:
mean diameter (mean) of 244 nm
minimum diameter (min) of 121 nm
maximum diameter (max) of 385 nm

The standard deviation (S.D.) is 5,3% and 70% of the particles posesses a diameter comprised between 180 and 300 nm.

Production example 2.

By means of the SAS technique amorphous or semicrystalline Nimesulide particles were produced. The substance was dissolved preferably in 1-methyl-2-pyrrolidone (NMP). The resulting solution should posess a concentration comprised between 0,1 and 100 mg/ml, preferably 10 mg/ml.
The solution is fed into the chamber at a flow rate between 0,1 and 10 ml/min, preferably at 1 ml/min, at a density of 1100 kg/m^3, in quantities ranging from 20 to 50 ml, preferably 30 ml.
The antisolvent, preferably carbon dioxide, is fed into the chamber at a flow rate comprised between 1000 and 10000 ml(gas STP)/min, preferably at 8000 ml (gas STP)/min and at a pressure between 80 and 200 bar, preferably 100 bar and at a temperature between 30 and 60 °C, preferably 40 °C. The resulting ratio between flow rate of solvent and flow rate of antisolvent is 1,25 E-04. The product is finally washed by passing only antisolvent through the chamber for a period of time ranging from 60 to 100 min, preferably 60 min.
Results:

- Yield:
  The yield of recovered Nimesulide (300 mg) was 93%.
- Identification based on physical data:
  The product collected from the bottom of chamber 1 was analyzed by means of scanning electron microscopy (SEM), with an magnification of 50000 X.

One is able to observe the remarkable homogeneity of the particle dimensions and their partial aggregation.

The particle diameter and the granulometric distribution were obtained from the SEM image by means of specific software (Sigma Scan 5.0). The spherical shape of the particles is typical of their amorphous state, as this subtance has needle shaped crystals in the crystalline state.

The granulometric distribution curve has the following characteristics:

mean diameter (mean) of 235 nm

minimum diameter (min) of 120 nm

maximum diameter (max) of 375 nm

The standard deviation (S.D.) is 5,8% and 70% of the particles posesses a diameter comprised between 180 and 300 nm.

CLAIMS

1. Product obtained by means of the micronization of pharmaceutical substances, characterized by solid amorphous and/or semicrystalline particles of micrometric and/or submicrometric dimensions, obtained by the action of a supercritical fluid which functions as an antisolvent.

2. The product of Claim 1, characterized by:
   a) particles posessing a diameter inferior to 4 μm; and
   b) a granulometric distribution, expressed as a standard deviation of less than 25%,preferably less than 20% ; and/or
   c) solid amorphous particles which are loose, partially aggregated or aggregated

3. The product of Claims 1 and 2, obtained by precipitation induced by the action of a supercritical antisolvent, into which the solvent of the solution containing the substance of interest swells and dissolves

4. The product of Claims 1 to 3 where the supercritical fluid is supercritical carbon dioxide and/or one of the following: nitrous oxide, propane, ethylene, water and/or trifluoromethane.

5. The product of Claims 1 to 4 where the solvent is 1-methyl-2-pyrrolidone and/or one of the following: dimethylsulfoxide, ethanol, acetone, ethyl acetate and/or dimethylformamide.

6. The product of Claims 1 to 5 where the micronized product be:
   a) Nimesulide, a derivative thereof or another sulfonamide or sulfone, inhibitors of cyclooxigenase (COX 1 and/or COX 2) belonging to the following therapeutic classes: antiinflammatories, antipyretics, analgesics, antirheumatics; and/or

b) sulfonamides or sulfones belonging to the following therapeutic classes : antibiotics, bacteriostatics, antihypertensives and diuretics.

7. A procedure in which a supercritical fluid mediated precipitation is used to produce pharmacologically active substances according to Claims 1 to 6

8. The procedure of Claim 7, according to which the substance, preferably a sulfonamide or sulfone, be produced in form of an amorphous and/or semicrystalline micronized powder starting from a solution of the said substance in an organic solvent, preferably dimethylsulfoxide, 1-methyl-2-pyrrolidone, ethanol, ethyl acetate or dimethylformamide

9. The procedure of Claims 7 and 8, where into a chamber is fed:
   a) a solution of Nimesulide whose concentration ranges from 0,1 to 100 mg/ml, at a flow rate ratio between flow rate of solution and flow rate of antisolvent comprised between 10^{-5} and 10^{-2} ml/min(gas STP); and/or
   b) an antisolvent at a pressure of between 78 and 400 bar and at a temperature comprised between 30 and 90 °C.

10. An apparatus to produce the product of Claims 1 to 6 or an apparatus performing the procedure according to Claims 7 to 9, characterized by:
   a) a precipitation chamber ; and
   b) a first injector coupled to a first pump, to deliver the solution; and
   c) a second injector coupled to second pump, to deliver the supercritical fluid

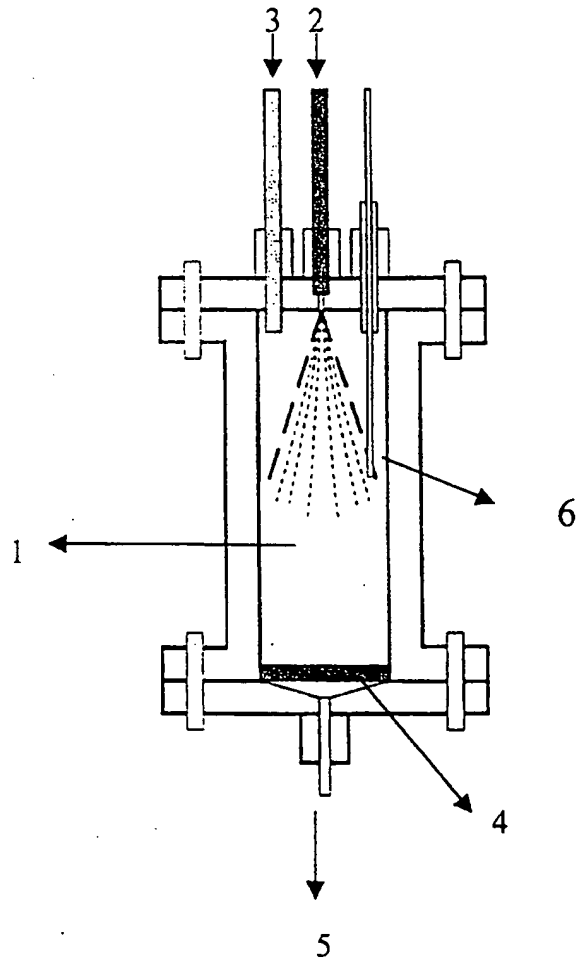

Fig. 1

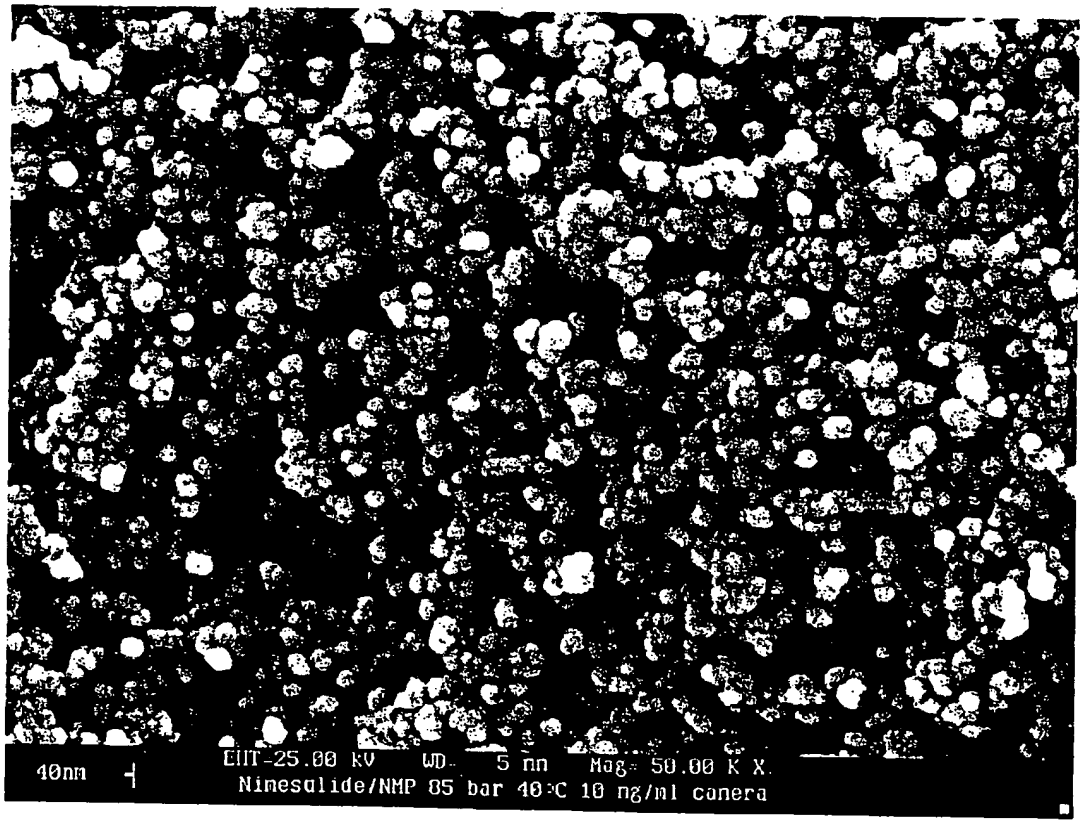
40nm
EHT=25.00 kV WD= 5 mm Mag= 50.00 K X
Nimesulide/NMP 85 bar 40°C 10 mg/ml canera

Fig. 2

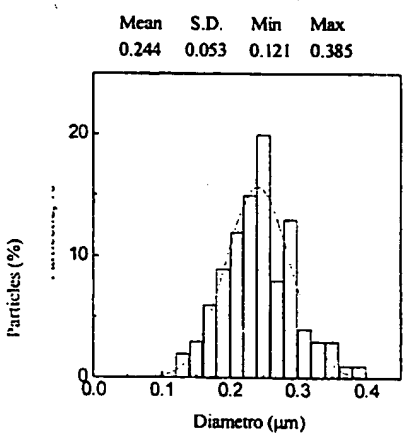
Mean S.D. Min Max
0.244 0.053 0.121 0.385
20
10
0
Particles (%)
0.0 0.1 0.2 0.3 0.4
Diametro (µm)

Fig. 3

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K9/16 A61K9/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 37169 A (SMITHKLINE BEECHAM) 29 June 2000 (2000-06-29) claims page 1, line 2 - line 12 page 4, line 31 -page 5, line 5 page 5, line 27 -page 6, line 4 page 6, line 18 - line 23 page 18, line 7 - line 9 examples ---	1-8,10
A	WO 97 14407 A (RESEARCH TRIANGLE PHARMACEUTICALS,U.S.A.) 24 April 1997 (1997-04-24) claims figures ---	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2001	20/07/2001

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir ational Application No
PCT/CH 01/00131

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ~	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 31691 A (UNIVERSITY OF KANSAS) 4 September 1997 (1997-09-04) claims figures 1-3,6 ---	1-10
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A	EP 0 542 314 A (PRINCETON UNIVERSITY) 19 May 1993 (1993-05-19) cited in the application claims figure 1 -----	1-10

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

I· ıational Application No
PCT/CH 01/00131

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